The efficacy of proton pump inhibitors for the treatment of asthma in adults: a meta-analysis

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CRD summary
This review concluded that proton-pump inhibitor therapy in adults with asthma resulted in a small improvement in the morning peak expiratory flow rate, but this was unlikely to be clinically meaningful. Despite some reporting limitations, the authors’ conclusions broadly reflected the evidence presented and are likely to be reliable.

Authors' objectives
To evaluate the efficacy of proton-pump inhibitors in asthma control for adults with or without symptomatic gastro-oesophageal reflux disease.

Searching
MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched, without language restrictions, to January 2010; search terms were reported. Reference lists of identified articles were examined to identify further studies.

Study selection
Randomised placebo-controlled trials investigating the efficacy of at least four weeks of daily therapy, using any proton-pump inhibitors alone to treat asthma, in adults (over 18 years old) were eligible. All participants had to have an asthma diagnosis established by their clinical history, a physician’s diagnosis, or evidence of variable expiratory airflow obstruction, such as change in peak expiratory flow rate or forced expiratory volume in one second (FEV\(_1\)). Trials had to report at least one clinical asthma outcome measure, such as peak expiratory flow rate, FEV\(_1\), asthma symptom score, or quality-of-life assessment; the morning peak expiratory flow rate was the primary outcome. Trials that did not demonstrate adequate randomisation were excluded as were those published only as abstracts.

Most trials were conducted in Europe or North America. In eight of them, a diagnosis of gastro-oesophageal reflux disease was required. Asthma diagnoses were based on a range of methods. Trials used omeprazole, lansoprazole, pantoprazole, esomeprazole, or rabeprazole, with an equivalent daily dose that ranged from 20mg to 80mg. Treatment duration ranged from four weeks to 26 weeks.

Two reviewers independently selected trials for inclusion.

Assessment of study quality
Trial quality was evaluated using criteria for the following: method of randomisation, method of allocation concealment, level of blinding, and duration of follow-up. They were also scored using the Jadad scale, which assesses randomisation, blinding, and withdrawals or drop-outs; the maximum score was five points and trials with a score of less than three were excluded from the review.

Two reviewers independently assessed trial quality, with disagreements resolved by a third reviewer.

Data extraction
Data were extracted to calculate mean differences and 95% confidence intervals between groups receiving proton-pump inhibitors and those receiving placebos.

Two reviewers independently extracted intention-to-treat data, with disagreements resolved by a third reviewer.

Methods of synthesis
The authors reported that meta-analyses were performed to calculate the pooled weighted mean differences and 95% confidence intervals, using a random-effects model. Heterogeneity was assessed using $I^2$. A subgroup analysis investigated any possible effect of trials that required a diagnosis of gastro-oesophageal reflux disease for inclusion compared with those that did not. Meta-regression was used to investigate any effect of different lengths of treatment, and drug dosage, and a cumulative analysis explored time trends by publication year. Sensitivity analyses were performed to examine the effect of removing single large trials. Publication bias was assessed using a funnel plot, and the trim-and-fill method.

**Results of the review**

Eleven trials with 2,524 participants (range nine to 960) were included; four had a cross-over design. All had the maximum Jadad score of five.

Patients receiving proton-pump inhibitors had a higher mean morning peak expiratory flow rate compared with the placebo group (WMD 8.68L per minute, 95% CI 2.35 to 15.02; nine trials; $I^2$=30%). There was no evidence of a relationship between treatment duration ($p=0.35$) and morning peak expiratory flow rate. The authors reported no significant relationship between morning peak expiratory flow rate and cumulative dose, as they defined significance as $p<0.05$; this meta-regression was significant at the $p=0.05$ level, with larger doses resulting in reduced mean differences. No significant effect of single large trials and no temporal effect were found. Subgroup analysis revealed a significantly larger improvement in morning peak expiratory flow rate in trials that only enrolled patients with gastro-oesophageal reflux disease (WMD 16.90L/min, 95% CI 0.85 to 32.95; seven trials) compared with those that did not (WMD 6.21L/min 95% CI 0.71 to 11.71; two trials). There was no evidence of significant publication bias.

There were no significant differences between groups in asthma symptom score, Asthma Quality of Life Questionnaire score, evening peak expiratory flow rate, FEV$_1$, and adverse events.

**Authors' conclusions**

Proton-pump inhibitor therapy in adults with asthma resulted in a small improvement in morning peak expiratory flow rate, which was unlikely to be clinically meaningful.

**CRD commentary**

The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify relevant trials in any language were made by searching electronic databases and checking references. The exclusion of trials reported only as abstracts means that some relevant data might have been missed. Suitable methods, such as independent duplicate processes, were used throughout the review to reduce the risk of reviewer error or bias. Trial quality was assessed, with all trials achieving the maximum score on the Jadad scale, but the results of the assessment of allocation concealment were not reported. Sufficient trial details were provided, and appropriate methods appear to have been used to pool the data and to assess heterogeneity. The authors did not report how the studies were weighted in the pooled analyses and the results of the heterogeneity tests were reported for only one analysis.

Despite some reporting limitations, the authors' conclusions broadly reflected the evidence presented, and are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that the routine use of proton-pump inhibitors in most patients with asthma was unlikely to result in significant clinical benefit. The relatively small improvements in morning peak expiratory flow rate should be assessed against the lack of improvement in the other objective and subjective asthma outcomes, as well as the risk of complications with chronic acid suppression.

**Research:** The authors stated that future studies should focus on clarifying the pathologic roles of symptomatic and silent gastro-oesophageal reflux disease in patients with asthma, exploring the clinical utility of physiological studies, such as oesophageal impedance and pH monitoring, and identifying subgroups of patients who could receive the most benefit from proton-pump inhibitor therapy.
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